Decreased Single-Photon Emission Computed Tomographic [^{123}I]β-CIT Striatal Uptake Correlates with Symptom Severity in Parkinson's Disease

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Previous studies have utilized single-photon emission computed tomography (SPECT) to demonstrate decreased [^{123}I]β-CIT striatal uptake in idiopathic Parkinson disease (PD) patients. The present study extends this work by examining SPECT outcome measures in a larger group of PD patients with varying disease severity. Twenty-eight L-dopa–responsive PD patients (Hoehn-Yahr stages 1–4) and 27 healthy controls had SPECT scans at 18 to 24 hours after injection of [^{123}I]β-CIT. Specific to nondisplaceable striatal uptake ratios (designated V_3'') were correlated with Hoehn-Yahr stage and Unified Parkinson's Disease Rating Scale (UPDRS) subscores. Linear discriminant function analyses utilizing striatal uptakes, putamen-to-caudate ratios, and ipsilateral–contralateral asymmetry indices were performed. Decreased striatal tracer uptake (V_3'') was correlated with total UPDRS score for both contralateral and ipsilateral striatum. Putamen uptake was relatively more reduced than caudate with mean putamen:caudate ratios of 0.50 ± 0.17 and 0.82 ± 0.09 for PD patients and controls, respectively. Ipsilateral:contralateral asymmetry was significantly greater in PD patients than controls. Discriminant function analysis utilizing V_3'' for ipsilateral and contralateral caudate and putamen correctly classified all 55 cases. These data demonstrate marked differences in [^{123}I]β-CIT SPECT measures in healthy controls and PD patients. The significant correlation of SPECT measures with motor severity suggests [^{123}I]β-CIT may be a useful marker of disease severity in PD.

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Parkinson's disease (PD) is characterized by an insidious onset with variable expression of motor symptoms and a slowly deteriorating course. Most patients present with unilateral symptoms that progress to bilateral disease [1]. The progression of motor symptoms in PD is reportedly due to ongoing losses of nigral dopaminergic neurons, although pathological confirmation of this hypothesis is limited. Postmortem data in PD patients have shown reduced dopamine (DA) content [2] and DA transporter density [3] in striatum with relatively greater abnormality in putamen compared with caudate [4]. Evaluation of disease progression based on clinical examination is complicated by the medication treatment of motor symptoms. Hence, the search for an objective marker of disease severity in PD is relevant to improved understanding of the pathophysiology of disease onset and progression and may provide clues to more accurate classification of phenomenologically distinct patient groups.

We have utilized [^{123}I]β-CIT [2β-carboxymethoxy-3β-(4[^{123}I]iodophenyl)tropane] in humans as a single-photon emission computed tomographic (SPECT) marker of DA transporters located on dopaminergic terminals in the striatum. Preliminary SPECT studies in healthy human subjects demonstrated high concentration of activity in striatum [5], a region rich in DA transporters, with stable levels of uptake for more than 24 hours after bolus intravenous administration of the radiotracer [6]. The protracted stability of [^{123}I]β-CIT striatal uptake permits measurement of a specific/nondisplaceable binding ratio, which is linearly related to B_{max}, the density of DA transporters [6]. The specific/nondisplaceable striatal binding ratio, designated V_3'', showed robust test/retest reproducibility in healthy

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subjects and PD patients [7]. In healthy human subjects, [^{123}I]β-CIT SPECT demonstrated reductions of tracer uptake with increasing age [8] compatible with postmortem reports of DA transporter loss in normal aging.

Initial studies of PD patients showed markedly abnormal striatal uptake, more pronounced in putamen than caudate, with larger decreases on the side contralateral to the side of greatest motor impairment [9, 10], consistent with changes described in positron emission tomographic (PET) studies in PD patients using the DA transporter agent [^{11}C]WIN 35,428 [11]. In a sample of 8 PD patients with exclusively unilateral symptoms, all 8 patients showed decreased striatal uptake on both the contralateral and ipsilateral sides compared with age- and gender-matched controls, suggesting [^{123}I]β-CIT SPECT may be sensitive to changes in DA transporter sites occurring prior to the onset of motor symptoms [12].

The purpose of the present investigation was to extend these preliminary data by examining a larger group of L-dopa–responsive PD patients with [^{123}I]β-CIT SPECT with the following questions: (1) Do SPECT outcome measures correlate with Hoehn-Yahr stage and Unified Parkinson's Disease Rating Scale (UPDRS) scores? (2) Are putamen:caudate ratios altered in PD patients? (3) Are ipsilateral:contralateral asymmetries of tracer uptake increased in PD patients? (4) What is the discriminative utility of SPECT measures of striatal uptake, putamen:caudate ratio, and asymmetry for distinguishing PD patients from controls?

Materials and Methods

Radiopharmaceutical Preparation

High specific activity [^{123}I]β-CIT was prepared from the corresponding trimethylstannyl precursor (Research Biochemicals International, Natick, MA) and high radionuclidic purity [^{123}I]NaI (Nordion International, Ltd, Vancouver, BC, Canada) as described previously [13, 14]. Radiochemical purity was 97 ± 2% (with these and subsequent measures expressed as mean ± SD) as measured with high-performance liquid chromatography (HPLC). Specific activity could not be directly measured but was more than 5,000 Ci/mmol.

Subjects

Twenty-eight patients (age, 63.0 ± 9.0 years) with idiopathic PD (Hoehn-Yahr stages 1–4) were enrolled in the study following the provision of informed consent. Inclusion criteria included age greater than 35 years and at least two of the following: bradykinesia, resting tremor, rigidity, postural instability, and freezing phenomena (one of which is rest tremor or bradykinesia). All patients were evaluated in the Yale-New Haven Hospital General Clinical Research Center using the modified CAPIT protocol [15]. Patients were evaluated using the UPDRS [16] and four timed motor tasks after 12-hour medication withdrawal and 1 hour following oral administration of carbidopa/L-dopa (25/100 mg). Response to L-dopa challenge was defined as a 33% improvement in UPDRS score or in one timed motor test. Patients who failed to respond were rechallenged with a repeat single oral dose of carbidopa/L-dopa (25/250 mg) and reexamined 1 hour later using these criteria. Those patients showing no response to L-dopa were excluded from the study. Patient characteristics and concomitant medications are described in Table 1.

Twenty-seven healthy controls (age, 52.5 ± 19.4 years) were recruited from Yale-New Haven Hospital, Yale University, and the community. Controls underwent a thorough history, physical examination, and laboratory evaluation prior to study enrollment. Subjects with first-degree family members with psychiatric or neurological illness were excluded. All subjects had negative urine toxicology screens and were taking no medication.

Data Acquisition and Analysis

All patients and healthy subjects received supersaturated potassium iodide solution (800 mg orally) prior to tracer injection. Four fiducial markers filled with 14 to 18 kBq (4–5 μCi) [^{99m}Tc]$NaTcO_4$ were attached to both sides of subjects' heads at the level of the canthomeatal line prior to imaging to facilitate post hoc computer reorientation of transaxial images. At 18, 21, and 24 hours following the intravenous bolus injection of 370 ± 57 MBq (10.0 ± 1.6 mCi) [^{123}I]β-CIT, SPECT scans were acquired in a 64 × 64 × 32 matrix on the Ceraspect device (Digital Scintigraphics, Waltham, MA), a head-dedicated SPECT tomograph with resolution of 7.5 to 8 mm full width half maximum (FWHM) in all three axes. Three 12- to 15-minute acquisitions were obtained at each of the three time points post injection.

Raw data were reconstructed from photopeak counts within a 20% symmetric energy window centered around 159 keV using a Butterworth filter (power factor = 10, cutoff = 1 cm). Transaxial images were reoriented parallel to the canthomeatal plane and attenuation-corrected using Chang zero-order correction [17] based on an ellipse fit to brain using a linear attenuation factor ($\mu = 0.15\ cm^{-1}$) determined empirically from an ^{123}I-containing distributed source phantom.

The striatal ratio of specific to nondisplaceable uptake, also designated V_3'', is proportional to the density of receptors (B_{max}) within the region of interest (ROI), if one assumes [^{123}I]β-CIT striatal uptake is unchanging over the time of imaging [6]. We believe this assumption is appropriate based on the extremely slow elimination rates of plasma parent compound, occipital, and striatal activity in previous human studies receiving bolus injections of [^{123}I]β-CIT and was confirmed in the present study by evaluation of scans obtained at different time points.

For calculating the ratio of striatal specific:nondisplaceable uptake (V_3''), four contiguous transaxial slices representing the most intense striatal uptake were summed. A standard region of interest template was constructed based on coregistered magnetic resonance imaging (MRI) scans obtained from previous [^{123}I]β-CIT studies in 4 healthy human controls. This template included regions for left and right caudate, putamen, and occipital cortex (Fig 1). Small variations in individuals' brains required movement of the ROIs within the template without changing the individual ROI shape or pixel area. Data were expressed as counts per minute per

Table 1. Patient Demographics

Patient	Age (yr)	Gender	Affected Side	Illness Duration (from Dx, in yr)	Hoehn-Yahr	Total UPDRS	L-Dopa/Carbidopa		DA Agonist			Selegiline
							Sinemet	Sinemet-CR	Amantadine	Pergolide	Bromocriptine	
1	54	M	L	7	3.0	47.5	400			3		10
2	62	F	L	2	2.0	42	450			2.25		
3	72	F	R	4	1.5	33.5						10
4	71	M	R	3.5	2	28.5	250	600				5
5	70	M	B	2.5	2.5	27.5	300					5
6	43	F	L	0.5	1	8.5	No meds					
7	53	M	R	2	1.5	20				1.5		10
8	71	M	R	4.5	2	46		800		0.75		10
9	69	M	R	0.5	1	21	No meds					
10	58	M	R	6	2	61	750				5	
11	74	F	L	0.5	1	29	No meds					
12	67	M	R	0.5	1.5	26.5	No meds					
13	66	F	L	4	2.5	44.5	300					
14	59	F	R	3.5	2	23.5	400					
15	65	M	L	8	4	61.5	750				3.75	5
16	60	M	R	3	1	13						2.5
17	50	F	R	9	4	97.5	1,000					
18	62	M	L	7	2.5	42.5		400				10
19	62	F	R	9	4	102	1,000					
20	75	M	L	3	4	76	400	300			2.5	10
21	62	M	R	4.5	2	38.5		600	200	2.25		10
22	58	M	L	6	2	57.5		800	300			
23	43	F	L	14	4	104.5	400			6	40	
24	66	M	L	8	2.5	39	300	600				5
25	75	M	L	3	2.5	34.5	150					10
26	63	M	L	3	2	29	200	300		3		10
27	78	F	L	6	3.5	58	450	300			20	
28	57	M	R	0.5	1	20	No meds					

Dx = diagnosis; UPDRS = Unified Parkinson's Disease Rating Scale; DA = dopamine; meds = medicine.

pixel (cpm/pixel) for each brain region. Estimates of striatal specific uptake were made by subtracting occipital cpm/pixel from total striatal cpm/pixel, based on the low density of monoamine transporters in the occipital lobe. This method assumes equivalence of nonspecific uptakes in striatum and occipital cortex. V_3'' was derived by dividing the striatal specific uptake by occipital uptake. The final ratio was calculated as the mean of all nine V_3'' measurements over 18, 21, and 24 hours (three scans at each time point).

V_3'' values were used to determine putamen:caudate activity ratios for ipsilateral and contralateral striatum. In the PD patients, the contralateral striatum was defined as the side opposite that of initial symptom presentation. All but 1 patient had a clearly identified side of initial symptom onset. For the control subjects, contralateral was arbitrarily assigned to the left striatum based on the lack of data clearly describing lateralized differences of striatal DA transporter density in humans. V_3'' was also used for calculating relative ipsilateral: contralateral asymmetry of uptake for caudate and putamen based on the following formula.

$$\text{Asymmetry Index (AI)} = \frac{\text{ipsilateral} - \text{contralateral}}{(\text{ipsilateral} + \text{contralateral})/2} \times 100$$

Statistical Analyses

V_3'' measures of contralateral putamen, ipsilateral putamen, contralateral caudate, and ipsilateral caudate were expressed as both the raw and age-corrected measure. Age correction was based on our previous finding of the sensitivity of [^{123}I]β-CIT striatal uptake (V_3'') to detect expected age-related reductions of striatal uptake in healthy humans [8]. Data were age corrected by fitting a regression line to the healthy control striatal data and correcting all V_3'' data with the regression function. Age-corrected data were expressed as the percentage of age-expected V_3'' value.

Descriptive statistics were performed on the V_3'', age-corrected V_3'', putamen:caudate ratio, and AIs in PD and healthy controls. Comparisons of patient and control SPECT measures (V_3'' with and without correction; putamen:caudate ratios; AIs) were made utilizing unpaired t tests with Bonferroni correction. Levene's test for the equality of variance was used for determination of the equivalence of the variance between groups and the appropriate variance was used based on the Levene test. All tests were two tailed with significance assessed at the $p < 0.05$ level. Correlation coefficients were calculated for the SPECT outcome measures and Hoehn-Yahr stage, total UPDRS score, UPDRS subscales (motor, bradykinesia, tremor).

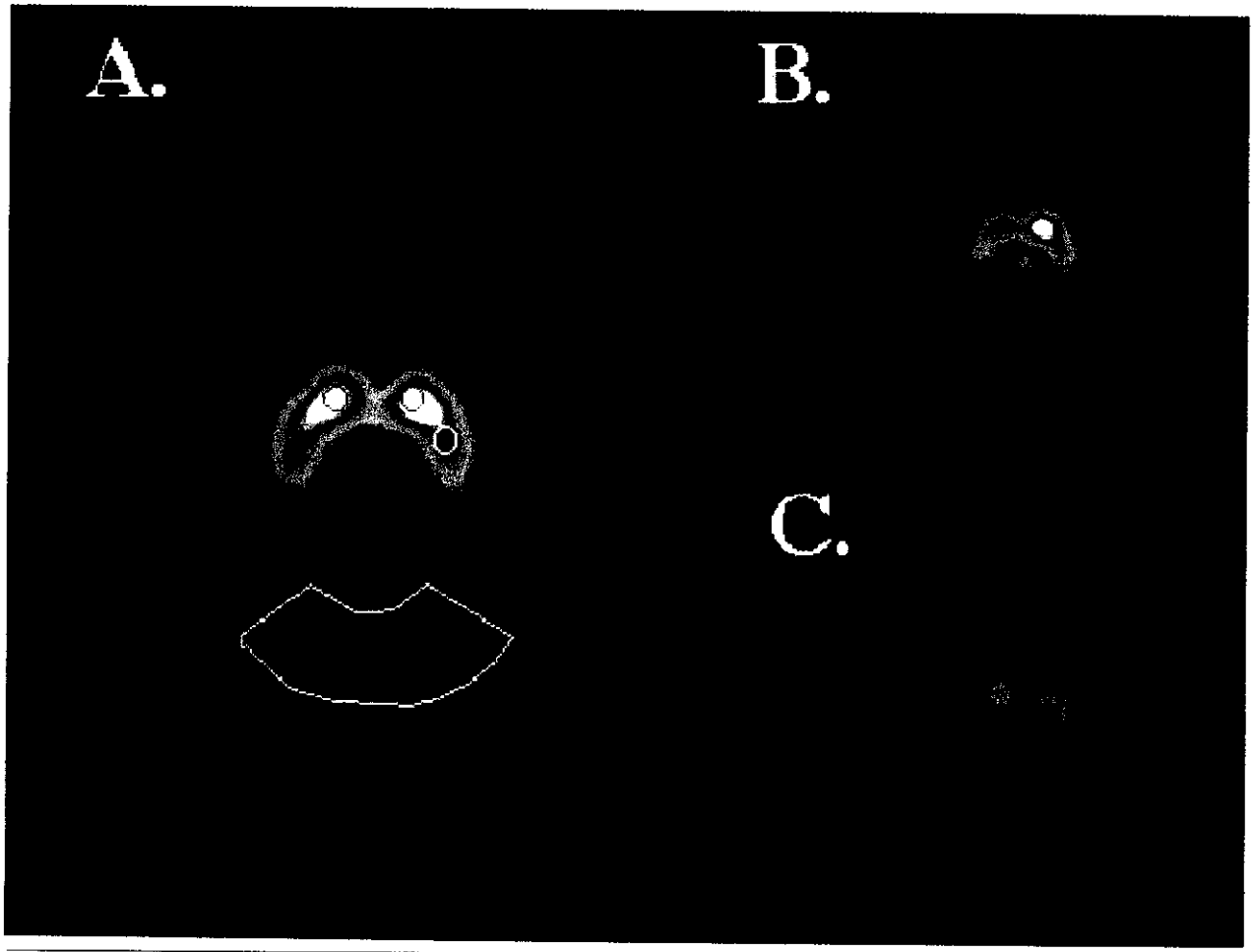


Fig 1. Transaxial single-photon emission computed tomographic images at the level of striatum in healthy control (A) and idiopathic Parkinson's disease subject Hoehn-Yahr stage 1 (B) and stage 4 (C) obtained at 24 hours following the injection of (^{123}I) β-CIT. The healthy subject scan demonstrates regions of interest placed in right and left caudate and putamen and occipital cortex.

The discriminative power of V_3'' (raw values and age corrected), putamen:caudate ratio, and AIs were analyzed using a linear discriminant function analysis utilizing SPSS/PC+ (SPSS, Inc, Chicago, IL) implemented on a Pentium computer platform. This analysis assesses the variance and discriminative power of each factor between groups accounting for the correlations, the univariate F ratio, and Wilks' Λ, a measure of the residual variance. Separate discriminant function analyses were applied to V_3'' (raw values), V_3'' (age-corrected values), putamen:caudate ratio, and AIs.

Results

Group Characteristics

χ^2 analysis found no significant gender differences between the control and PD patient groups ($p = 0.51$). However, there were significant age differences between controls and PD patients, with the control group younger (52.5 ± 19.4 years) than the PD group (63.0 ± 9.1 years) ($t = 2.57$, $p = 0.014$). Within the PD group, 14 patients had initial left-sided motor symptoms, 13 had right-sided onset, and 1 patient had bilateral symptom onset.

Comparison of Control and PD SPECT Values—Descriptive Measures

Comparisons between PD patient and control SPECT measurements are summarized in Table 2. Unpaired t tests demonstrate significant between-group differences for all four V_3'' measures (ipsilateral putamen, contralateral putamen, ipsilateral caudate, contralateral caudate), both with and without age correction. Bonferroni correction for the number of tests run yields p values that are all less than 0.01. The age-corrected putamen V_3'' measures are indicated in Figure 2. A few control subjects showed overlap with the PD group on the age-corrected data. Within the PD group, there were significant contralateral/ipsilateral differences ($p = 0.00003$ and $p = 0.0094$ for caudate and putamen, respectively). The controls also showed greater V_3'' measures for left caudate and putamen compared with

Table 2. Parkinson's Disease Patient and Control (^{123}I) β-CIT Single-Photon Emission Computed Tomographic Measures

	V_3''				V_3'' Age-corrected, Percentage of Expected Value				Putamen:Caudate Ratio		Asymmetry Index	
	Ipsi Caudate	Ipsi Putamen	Contra Caudate	Contra Putamen	Ipsi Caudate	Ipsi Putamen	Contra Caudate	Contra Putamen	Ipsilateral	Contralateral	Caudate	Putamen
PD patients	5.59	2.93	4.71	2.29	55.5%	37.5%	46.9%	29.5%	0.51	0.50	23.1	40.1
SD	±2.63	±1.73	±2.42	±1.20	±25.6%	±21.3%	±24.1%	±15.9%	±0.10	±0.17	±17.6	±22.7
Controls	10.89	8.4	11.42	9.33	98.0%	94.8%	103.1%	105.3%	0.77	0.82	7.2	14.6
SD	±3.13	±2.52	±2.87	±2.54	±25.9%	±23.0%	±22.8%	±20.5%	±0.11	±0.09	±4.9	±13.0
t	6.81	9.34	9.38	9.58	6.11	9.58	8.85	15.33	9.15	8.59	4.6	5.13
Two-tailed significance	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$

Note: For healthy subjects ipsilateral is arbitrarily assigned to right striatum.
Ipsi = ipsilateral; Contra = contralateral.

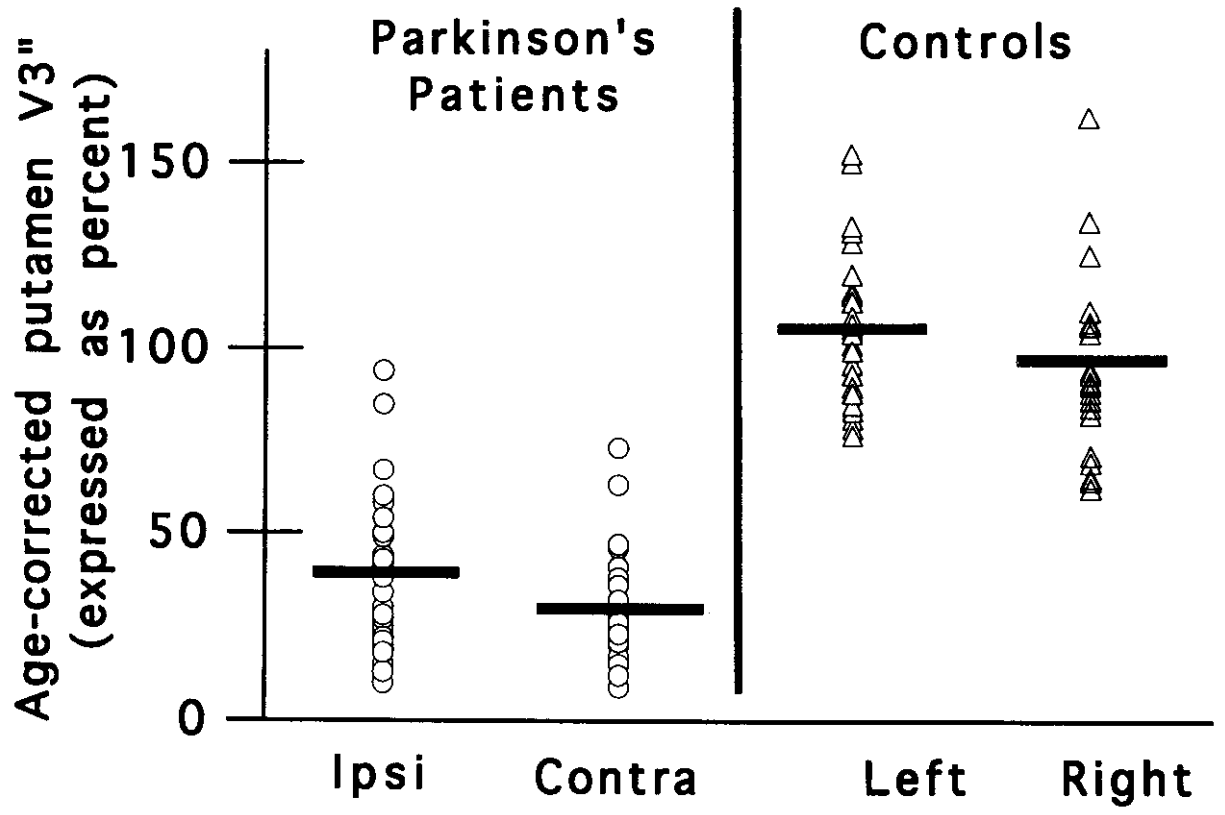


Fig 2. Striatal specific:nondisplaceable binding ratio (V_3'') measures expressed as a percentage of the age-expected value in ipsilateral and contralateral putamen in idiopathic Parkinson's disease (PD) patients and controls. Bars indicate the mean values based on age correction to a linear regression of the healthy subject data. The contralateral putamen in PD patients (mean, 30% of age-expected control value) shows greater reduction than ipsilateral (mean, 38% of control).

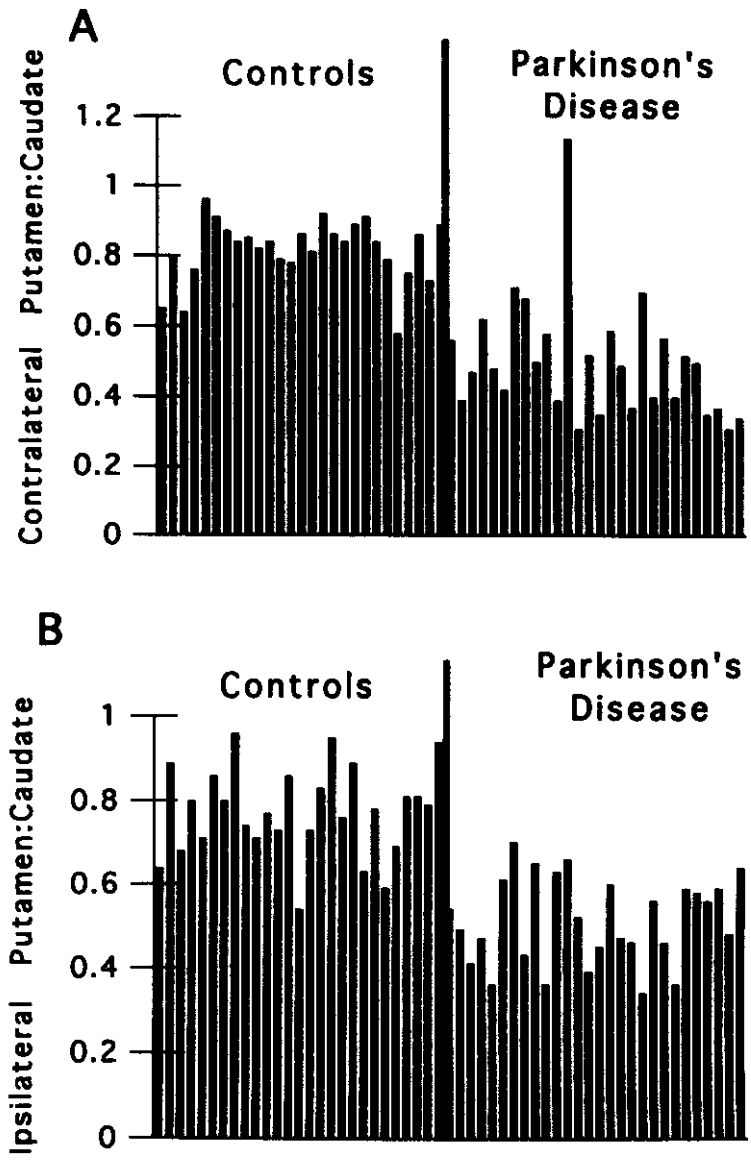


Fig 3. Putamen:caudate ratios of V_3'' values for contralateral and ipsilateral sides in individual Parkinson's disease patients and controls. Ipsilateral was arbitrarily assigned to right striatum in the controls. Patients demonstrate significantly reduced ratios compared with controls, suggesting relatively greater reduction in putamenal uptake compared with caudate.

the right ($p = 0.0017$ and $p = 0.0011$, caudate and putamen, respectively).

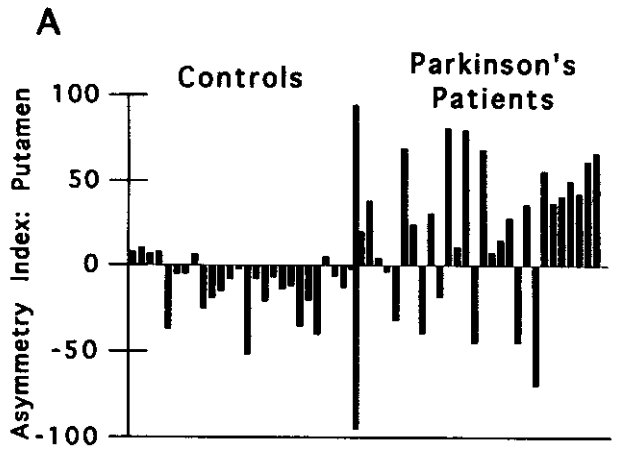
Putamen:caudate ratios were significantly different between the PD and control groups (see Table 2, Fig 3). Within-group comparisons showed no differences in the ipsilateral and contralateral ratios for either the PD or controls ($p = 0.7745$ and $p = 0.074$, PD and controls, respectively).

AIs were significantly different between PD and control groups for both caudate and putamen (see Table 2, Fig 4). Within the PD group, the putamen showed greater asymmetry than caudate ($p = 0.0013$). The control group demonstrated significantly more negative AI values in both caudate and putamen ($p = 0.0014$ and $p = 0.0015$, caudate and putamen, respectively), indicating that left striatal uptake was greater than right.

Correlation of SPECT with Motor Symptoms

Hoehn-Yahr stage, total UPDRS, motor UPDRS, and UPDRS bradykinesia measures were all significantly correlated with age-corrected V_3'' (Table 3, Fig 5). Tremor ratings were not correlated with SPECT measures.

Putamen:caudate ratios were significantly correlated with total UPDRS score for the ipsilateral but not the contralateral values. The ipsilateral putamen:caudate



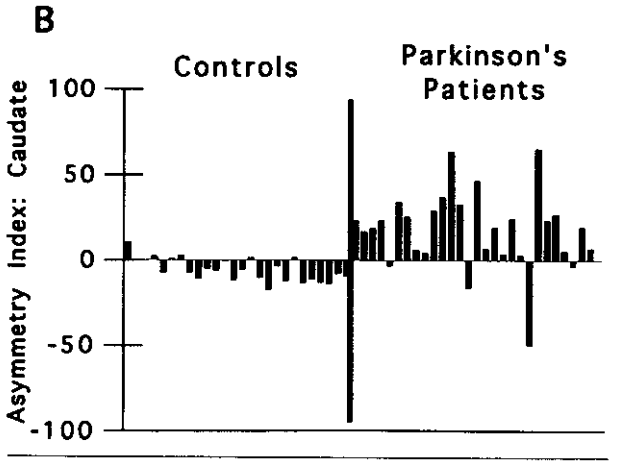


Fig 4. Putamen and caudate asymmetry index (see text for description) in healthy and Parkinson's disease patients. Patients demonstrate significantly greater asymmetry in both putamen and caudate than control subjects.

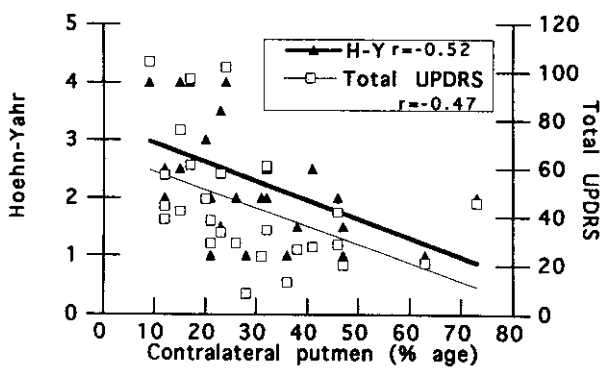


Fig 5. Correlation of Hoehn-Yahr stage and total Unified Parkinson's Disease Rating Scale score with age-corrected contralateral V_3'' values for individual idiopathic Parkinson's disease patients.

ratio showed a nonsignificant trend for correlation for Hoehn-Yahr stage, motor UPDRS scores, and bradykinesia. Contralateral putamen:caudate ratios were not correlated with Hoehn-Yahr stage or UPDRS score or subscores.

The AI calculated between caudate and putamen were not correlated with Hoehn-Yahr stage or UPDRS scores. The caudate AI showed a modest, but significant, correlation with tremor score.

Discriminant Function Analyses

Separate discriminant function analyses in PD patients and controls were performed for V_3'' values in the following four categories: contralateral and ipsilateral caudate and putamen, age-corrected V_3'' values, putamen:caudate ratios, and AI (Table 4). The individual measures employed in each analysis are indicated in the

Table 3. Correlation Coefficients for Single-Photon Emission Computed Tomographic Measures and Motor Ratings in Parkinson's Disease Patients

	V_3''				Putamen:Caudate Ratio		Asymmetry Index	
	Ipsi Caudate	Ipsi Putamen	Contra Caudate	Contra Putamen	Ipsilateral	Contralateral	Caudate	Putamen
H-Y score	−0.507	−0.576	−0.482	−0.517	−0.364	−0.155	−0.031	0.025
p	0.006	0.001	0.009	0.005	0.057	0.430	0.876	0.898
Total UPDRS	−0.480	−0.551	−0.494	−0.472	−0.386	−0.944	0.089	−0.016
p	0.010	0.002	0.008	0.011	0.043	0.823	0.652	0.936
Motor UPDRS	−0.467	−0.525	−0.478	−0.468	−0.354	−0.058	0.080	−0.011
p	0.012	0.004	0.01	0.012	0.065	0.767	0.685	0.956
Bradykinesia	−0.464	−0.521	−0.473	−0.481	−0.335	−0.086	0.050	−0.006
p	0.013	0.004	0.011	0.010	0.081	0.662	0.799	0.975
Tremor	−0.122	−0.200	−0.164	−0.091	−0.298	−0.004	0.410	0.113
p	0.536	0.308	0.405	0.646	0.124	0.984	0.030	0.568

Note: Correlations are for age-corrected values.
Ipsi = ipsilateral; Contra = contralateral; H-Y = Hoehn-Yahr; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 4. Discriminant Function Analyses in Parkinson's Disease Patients and Controls

Analysis	Factors	Within Function Correlation	Univariate *F* Ratio	Wilks' Λ		Percentage of Cases Correctly Assigned
				Factor	Overall	
A	Contralateral putamen	0.86	174.3[a]	0.233	0.184	98
V_3'' values	Contralateral caudate	0.61	88.0[a]	0.376		
	Ipsilateral putamen	0.61	88.4[a]	0.375		
	Ipsilateral caudate	0.44	46.4[a]	0.533		
B	Contralateral putamen	0.79	235.0[a]	0.184	0.124	100
V_3'' values	Contralateral caudate	0.49	78.3[a]	0.404		
(age-corrected)	Ipsilateral putamen	0.46	91.8[a]	0.366		
	Ipsilateral caudate	0.32	37.4[a]	0.586		
C	Contralateral ratio	0.73	76.4[a]	0.409	0.270	96
Putamen:caudate ratio	Ipsilateral ratio	0.74	79.0[a]	0.401		
D	Caudate asymmetry index	0.73	20.5[a]	0.721	0.58	80
Asymmetry index	Putamen asymmetry index	0.82	25.8[a]	0.672		

[a] $p < 0.0001$, Parkinson's disease vs controls.

table. For raw V_3'' measures, the contralateral putamen value demonstrated the strongest loading ($r = 0.86$), with a univariate F ratio = 174, supporting the notion that contralateral putamen accounts for the greatest difference between the PD and control groups for the four V_3'' measures. The Wilks' Λ for contralateral putamen suggested this measure accounted for most of the variance between PD and controls. Ipsilateral putamen and contralateral caudate showed a similar high loading ($r = 0.61$), magnitude of F ratio, and Wilks' Λ, indicating measures from these two regions are roughly equivalent for distinguishing patients and controls and not as sensitive as the contralateral putamen measure. Ipsilateral caudate showed the least discrimination between groups, although the F ratio between the controls and PD patients was still significant at the $p < 0.0001$ level. Overall, utilizing the four raw V_3'' factors resulted in highly significant discrimination between groups. Using the discriminant function, the model predicted correct group membership in 54 of the 55 cases (98%).

Age correction of the V_3'' factors reduced the unaccounted-for variance between the PD and control groups and accurately assigned 55 of 55 cases (100%). Loading again demonstrated the greatest discrimination was from the contralateral putamen, followed by roughly equal loading for contralateral caudate and ipsilateral putamen, followed by ipsilateral caudate.

Putamen:caudate ratios taken alone were slightly less discriminative than V_3'' values. Ninety-six percent of the cases were accurately assigned by the discriminant model. There was no difference between the ipsilateral and contralateral ratios in either loading or individual Wilks' Λ values.

The AI proved the least discriminating between the PD and control groups. The discriminant function using AI alone assigned 80% of cases to the correct diagnostic group.

Discussion

These data describe marked and significant differences between 28 L-dopa–responsive PD patients and 27 healthy controls on the following three [^{123}I]β-CIT SPECT measures: V_3'' (raw and age-corrected values), putamen:caudate ratios, and ipsilateral:contralateral asymmetry. Hoehn-Yahr stage and UPDRS scores were significantly correlated with V_3'' measured in ipsilateral and contralateral putamen and caudate. Putamen:caudate ratios showed only a trend toward significant correlation with motor measures for the ipsilateral side. AIs did not correlate with motor scores. For the PD patient group, the differential reductions of V_3'' in distinct striatal regions were in the expected order with the greatest reduction in contralateral putamen (mean reduction, 30% of control), then ipsilateral putamen (38%), then contralateral caudate (47%), and finally, ipsilateral caudate (56%). Discriminant function analysis using age-corrected V_3'' values was able to correctly discriminate all PD patients and controls. While significantly different relative to control group, the additional measures of putamen:caudate ratio and AIs were less successful than V_3'' in discriminating the groups.

What is the best [^{123}I]β-CIT outcome measure for evaluation of DA transporter loss in PD? On the basis of these data, age-corrected V_3'' provides the highest degree of discrimination for the evaluated measures. The contralateral putamenal value alone accounted for 82% of the between-group variance. This suggests that a simple ratio obtained in putamen on the day after radiotracer injection (18–24 hours) is both highly discriminatory and well correlated with symptom severity

measures. Other measures (putamen:caudate ratio and AI) may prove more useful in the differentiation of idiopathic PD patients from Parkinson syndrome patients rather than in the serial evaluation of disease progression in idiopathic PD. The diagnostic utility of the putamen:caudate ratio and AI is currently being evaluated by our group in Parkinson syndrome patients.

The poor correlation of tremor ratings with SPECT measures is not surprising given the poor clinical correlation of tremor with disease severity and the fact that the UPDRS is weighted toward assessment of bradykinesia. On the other hand, bradykinesia has been shown to be highly correlated with clinical severity and abnormal PET [^{18}F]dopa uptake [18]. In the present study, bradykinesia ratings were also highly correlated with SPECT V_3'' measures. Of interest is the correlation between the ipsilateral putamen:caudate ratio and UPDRS score, but not contralateral putamen:caudate ratio. This may represent a "pseudonormalization" of the putamen:caudate ratio on the more affected side.

PET studies of [^{18}F]dopa uptake in striatum have been the gold standard of functional evaluation of nigral DA neuron function in PD. While measuring a different aspect of dopaminergic pathophysiology, the present study utilizing [^{123}I]β-CIT SPECT is consistent with the PET [^{18}F]dopa studies including the demonstration of relatively greater putamenal abnormality compared with caudate, ipsilateral/contralateral asymmetries, and correlation with symptom severity [19–21]. [^{123}I]β-CIT SPECT also shows the expected reduction of uptake in normal aging brain. Both [^{123}I]β-CIT SPECT [12] and [^{18}F]dopa PET [19, 20, 22] are sensitive to changes in DA function occurring prior to the onset of clinical symptoms. One major advantage of [^{123}I]β-CIT SPECT for potential clinical application lies in the ready availability of SPECT instruments.

These data must be viewed in light of several possible sources of error. First, care was taken to develop ROIs small enough to provide accurate separation of caudate and putamen. The risk of such a strategy is the relatively greater statistical variation associated with V_3'' compared with larger ROIs. In a pilot analysis of 12 PD patients and 12 controls from the present data, we examined a larger ROI template derived from coregistered MRI image for analyzing activity within caudate and putamen. The larger ROIs showed smaller coefficients of variation (COVs) for the mean of V_3'' measurement taken within each subject's scanning session compared with the COV for the same scans analyzed with the standard ROI used in this study (%COV = 18 ± 6% and 9 ± 3% for standard and larger ROIs in healthy subjects, respectively; %COV = 28 ± 16% and 10 ± 4% for standard and larger ROIs in PD patients, respectively). Nonetheless, V_3'' values obtained with larger ROIs are lower, due to significant volume averaging. In addition, there was greater within-subject noise in the putamen:caudate ratio data for the larger ROI, possibly due to the contamination of putamen with caudate counts and uncertainty in precisely placing the ROI template to accurately separate these structures. The ROI strategy employed in the present data (see Fig 1) provides for cleaner separation of caudate and putamen. Further improvements in SPECT instrumentation may permit greater spatial resolution, reduce partial volume errors, and thereby provide caudate and putamen V_3'' measurements closer to the actual values.

Another source of possible confounding in these data lies in the fact that PD patients were medicated. It is possible that direct or indirect effects of medications on the DA transporter could interfere with V_3'' measurements. An in vitro study demonstrated relatively weak inhibitory effects of L-deprenyl and potent effects of D-deprenyl on the selective DA transporter inhibitor [^{3}H]GBR-12935 binding in rat striatal slices [23]. In addition, nonspecific effects of L-dopa could interfere with [^{123}I]β-CIT binding. In preliminary baboon studies we were unable to produce displacement of activity from brain in animals receiving suprathera-peutic L-dopa/peripheral dopa decarboxylase inhibitor infusions during the plateau phase of [^{123}I]β-CIT imaging [24]. In the present study, review of striatal [^{123}I]β-CIT uptake in the 5 unmedicated patients did not demonstrate differences from other Hoehn-Yahr stage 1 patients receiving medications. Nonetheless, the effects of medication treatment were not addressed in this study, and we are currently studying the effects of L-dopa on [^{123}I]β-CIT SPECT imaging in early PD patients.

The mean age of the healthy control group was significantly less than that of the PD patient group. For uncorrected data, this could have the effect of increasing the significance of the difference between the groups, although in the discriminant function analysis, the raw V_3'' data showed slightly poorer separation of the groups than age-corrected V_3'' (see Table 4). Regardless, the sensitivity of [^{123}I]β-CIT SPECT for detecting expected age-related reductions of DA transporter density makes age correction useful when comparing groups that are not age matched. The age-correction algorithm utilized in this study was based on the linear regression of the healthy subject V_3'' data. The small number of healthy subjects used in this analysis could generate error in the correction. The method itself assumes a linear reduction of DA transporter density with age, which may not accurately reflect this process.

An unexpected finding in the healthy group was the relative left/right striatal difference seen in V_3'' and AIs (see Table 2, Fig 4). Peterson and colleagues [25]

have reported significantly larger left basal ganglia size in right-handed healthy controls including lenticular nuclei measured with volumetric MRI, although postmortem data have not shown unequivocable left/right striatal volume differences [26]. Left/right differences within the healthy group may have been contributed to actual volume differences, resulting in differential partial volume averaging of the SPECT signal and/or actual reductions in DA transporters. The fact that the healthy group was not well characterized with regard to cerebral dominance makes this an interesting observation of uncertain significance.

In summary, these data demonstrated marked differences in [^{123}I]β-CIT SPECT measures in healthy controls and PD patients with a very high degree of separation between the two groups using a discriminant function analysis. In each of the 55 subjects studied, age-corrected [^{123}I]β-CIT uptake in caudate and putamen accurately identified the subject as either normal or Parkinson. Age-corrected V_3'' in the putamen contralateral to the side of symptom onset provided particularly good group separation with only 18% unaccounted variance. Further, the significant correlation of SPECT measures with motor ratings suggests [^{123}I]β-CIT may be a useful marker of disease severity in PD with potential utility in serially monitoring disease progression.

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References

1. Hoehn M, Yahr M. Parkinsonism: onset, progression, and mortality. Neurology 1967;17:427–442
2. Bernheimer H, Birkmayer W, Hornykiewicz O, et al. Brain dopamine and the syndromes of Parkinson and Huntington: clinical, morphological, and neurochemical correlations. J Neurol Sci 1973;20:415–455
3. Kaufman MJ, Madras B. Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's-diseased striatum. Synapse 1991;9:43–49
4. Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. N Engl J Med 1988;318:876–880
5. Seibyl J, Wallace E, Smith E, et al. Whole body biodistribution, radiation absorbed dose, and brain SPECT imaging with [^{123}I]β-CIT in healthy human subjects. J Nucl Med 1994;35:764–770
6. Laruelle M, Wallace E, Seibyl J, et al. Graphical, kinetic, and equilibrium analyses of in vivo [^{123}I]β-CIT binding to dopamine transporters in healthy human subjects. J Cereb Blood Flow Metab 1994;14:982–994
7. Seibyl J, Marek K, Smith E, et al. Decreased [^{123}I]β-CIT SPECT striatal uptake correlates with disease severity on idiopathic Parkinson's disease. Soc Neurosci Abstr 1994;20:1464 (Abstract)
8. van Dyck C, Seibyl J, Malison R, et al. Age-related decline in dopamine transporter binding in human striatum with [^{123}I]β-CIT SPECT. J Nucl Med 1995;36:1175–1181
9. Innis R, Seibyl J, Scanley B, et al. SPECT imaging demonstrates loss of striatal monoamine transporters in Parkinson's disease. Proc Natl Acad Sci USA 1993;90:11965–11969
10. Brücke T, Kornhuber J, Angelberger P, et al. SPECT imaging of dopamine and serotonin transporters with [^{123}I]β-CIT binding kinetics in the human brain. J Neural Transm Gen Sect 1993;94: 137–146
11. Frost J, Rosier A, Reich S, et al. Positron emission tomographic imaging of the dopamine transporter with C-11-WIN 35,428 reveals marked declines in mild Parkinson's disease. Ann Neurol 1993;34:423–431
12. Marek KL, Seibyl JP, Zoghbi SS, et al. [^{123}I]β-CIT SPECT imaging demonstrates bilateral loss of dopamine transporters in hemiparkinson's disease. Neurology (In press)
13. Baldwin R, Zea-Ponce Y, Zoghbi S, et al. Evaluation of the monoamine uptake site ligand [^{123}I]methyl 3β-(4-iodophenyl)-tropane-2β-carboxylate (^{123}I)β-CIT in non-human primates: pharmacokinetics, biodistribution and SPECT brain imaging co-registered with MRI. Nucl Med Biol 1993;20:597–606
14. Neumeyer JL, Wang S, Milius RA, et al. [^{123}I]-2-β-Carbomethoxy-3-β-(4-iodophenyl)tropane (β-CIT): high affinity SPECT radiotracer of monoamine reuptake sites in brain. J Med Chem 1991;34:3144–3146
15. Langston J, Widner H, Goetz C, et al. Core assessment program for intracerebral transplantations (CAPIT). Mov Disord 1992;7: 2–13
16. Fahn S, Elton R, Members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease. Florham Park, NJ: Macmillan Healthcare Information, 1987:153–164
17. Chang L. A method for attenuation correction in computed tomography. IEEE Trans Nucl Sci 1987;NS-25:638–643
18. Eidelberg D, Moeller I, Dhawan V, et al. The metabolic anatomy of Parkinson's disease: complementary [18F]fluorodeoxyglucose and [18F]fluorodopa positron emission tomographic studies. Mov Disord 1990;5:203–213
19. Garnett ES, Nahmias C, Firnau G. Central dopaminergic pathways in hemiparkinsonism examined by positron emission tomography. Can J Neurol Sci 1984;11:174–179
20. Nahmias C, Garnett ES, Firnau G, et al. Striatal dopamine distribution in parkinsonian patients during life. J Neurol Sci 1985; 69:223–230
21. Brooks DJ, Ibanez V, Sawle GV, et al. Differing patterns of striatal ^{18}F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. Ann Neurol 1990; 28:547–555
22. Calne DB, Langston JW, Martin WR, et al. Positron emission tomography after MPTP: observations relating to the cause of Parkinson's disease. Nature 1985;317:246–248
23. Fang J, Yu P. Effect of L-deprenyl, its structural analogues and some monoamine oxidase inhibitors on dopamine uptake. Neuropharmacology 1994;33:763–768
24. Laruelle M, Baldwin R, Malison R, et al. SPECT imaging of dopamine and serotonin transporters with [^{123}I]β-CIT: pharmacological characterization of brain uptake in nonhuman primates. Synapse 1993;13:295–309
25. Peterson B, Riddle M, Cohen D, et al. Human basal ganglia asymmetries on magnetic resonance images. Magn Res Imaging 1993;11:493–498
26. Bøttcher J. Morphology of the basal ganglia in Parkinson's disease. Acta Neurol Scand 1975;52:1–85